REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicants wish to thank Examiners Jones and Chakrabarti for the courtesy extended to applicants' representatives during the December 4, 2001, personal interview. Present on behalf of the applicants were: Dr. Notomi (inventor), Mr. Kojiya, and Mr. Yazawa, all of Eiken Chemical Co. Ltd., the assignee of record, as well as Mr. Goldman and the undersigned, both attorneys of record. The outcome of the personal interview is summarized below.

Pursuant to 37 CFR § 1.21, attached as an Appendix is a version of the amended claims and specification which contains markings to show the changes made.

The rejection of claims 29-50 under 35 U.S.C. § 112 (second paragraph) for indefiniteness is respectfully traversed in view of the above amendments.

During the personal interview, an issue was raised concerning written descriptive support for the amendments now made to claim 29. As discussed during the personal interview, written descriptive support for the amendments made to claim 29 (as well as new claim 51) is provided in Figures 1-3, which illustrate the claimed methods. The structure recited in step A) of both amended claim 29 and new claim 51 is illustrated in Figure 2 at (7). This structure includes a 3' end portion which includes complementary regions F1 (3' terminal) and F1c that are capable of annealing to one another to form a first loop that contains region F2c; and a 5' portion which includes complementary regions R1 and R1c (5' terminal) that are capable of annealing to one another to form a second loop that contains region R2. Illustrated in Figure 2 at (7) is the beginning of the 3' terminal extension, initiated from the 3' terminal of F1 as depicted by the arrow. This extension is carried out by a polymerase having strand displacement activity, such that the polymerase opens the second loop formed by R1 and R1c, allowing extension of the 3' terminal to proceed to the 5' end of this nucleic acid. Extension to the 5' end is indicated by the structure shown in Figure 3 at (8) containing, within the extended portion, complementary regions R1 (3' terminal) and R1c that are capable of annealing to one another to form a third loop that contains region R2c. (This extended portion containing R1(3' terminal), R2c, and R1c is complementary to the 5'

end portion of the structure shown in Figure 2 at (7), which contains R1c (5' terminal), R2, and R1.) As shown in Figure 3 at (8), extension of an oligonucleotide primer FA, which was annealed to the first loop F2c in Figure 2 at (7), has resulted in the displacement of this extended portion, allowing R1 (3' terminal) and R1c to anneal to form a third loop. As a result of the annealing between R1 and R1c to form the third loop, further extension at the 3' terminal occurs to the 5' end of this extended structure via a polymerase having strand displacement activity, resulting in formation of the structure shown in Figure 3 at (9) and the displacement of the extension product of the annealed oligonucleotide primer shown in Figure 3 (at (8) while annealed and at (10) once displaced). That this process can be repeated is recited at page 29, lines 2-9, which indicates that a nucleic acid complementary to a template can also be used as a template; at page 42, lines 6-8, which indicates that the structure shown in Figure 3 at (10) can function as a new nucleic acid involved in self-elongation and new nucleic acid formation; and at page 44, last paragraph, which indicates that a series of these reactions can proceed under the conditions described.

Since written descriptive support is present for all limitations appearing in claims 29 and 51, as well as all claims dependent thereon, applicants have amended the specification to more clearly recite which regions shown in Figures 2 and 3 correspond to the first, second, and third loops as recited in the claims. Because written descriptive support exists, no new matter has been entered as a result of these amendments to the specification.

The rejection of claims 29-41 and 45-50 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 5,874,260 to Cleuziat et al. ("Cleuziat") in view of U.S. Patent No. 5,612,199 to Western et al. ("Western") is respectfully traversed.

Cleuziat relates to a method of synthesizing a nucleic acid by cyclic amplification of a target sequence. Amplification is primed by an oligonucleotide primer containing (i) a stem and loop (or hairpin) structure at the 5' end of the oligonucleotide, which includes a blocking agent that precludes extension of a synthesized complementary strand by a polymerase; (ii) a segment capable of hybridizing to a target nucleic acid, which segment is <u>not</u> part of the stem; and, optionally, (iii) a segment which acts as a promoter for RNA polymerase (Cleuziat, Figure 1, col. 8, lines 33-44 and col. 11, lines 1-40). Origin of synthesis occurs at the 3' end of the oligonucleotide primer; however, the 3' end of the primer does not form any part of the stem. During initial synthesis steps (Cleuziat, Figure 4A), the oligonucleotide primer hybridizes to the target nucleic acid which is to be copied, affording strands II, II' and, subsequently, strands IV, IV'. However, the presence of the

blocking agent absolutely precludes formation of a complementary strand which includes a stem/loop structure at both the 5' end and the 3' end, because a template which contains a stem/loop formation at its 5' end is never fully copied beyond the loop region due to the presence of a blocking agent (see Cleuziat, Figures 4A-B and col. 16, line 8-12). Thus, Cleuziat alone never teaches formation of a nucleic acid which includes a stem/loop formation at both its 5' end and its 3' end.

Western provides a system and method for preparing a primer used in a single-primer amplification procedure. The system results in either extension of an initial probe or modification of the 3' end of probes, such that all that remains from an initial process is a single set of extension products that can be used as primers in a single-primer amplification procedure. Specifically, at col. 14, line 36 to col. 15, lines 23, Western described various approaches for rendering probes which do not hybridize to the target, ineffective for the subsequent single-primer amplification (i.e., essentially neutralizing the contents of the reaction medium such that only the single primer remains). According to one approach, the 3' end of non-hybridizing, non-extended probes is degraded using an exonuclease (see Western, Figs. 4-5 and col. 14, lines 56-67). According to another approach, the 3' end of non-hybridizing probes is hybridized to a scavenger and extended such that it cannot hybridize to a subsequent target nucleic acid (see Western, Fig. 1 and Fig. 3). Regardless of the approach, nowhere does Western suggest formation of a nucleic acid molecule having a 3' end portion which includes a stem/loop formation, let alone a nucleic acid molecule having both a 3' end portion which includes a stem/loop formation and a 5' end portion which includes a stem/loop formation.

Although the PTO previously acknowledged at page 6 of the outstanding office action that Cleuziat did not teach or suggest a nucleic acid having a stem/loop formation at both its 3' end and its 5' end, the PTO suggested that Western overcomes this deficiency, citing to Figure 5 and col. 14, lines 36-44 of Western. Figure 5 illustrates one embodiment of Western whereby a probe (5'-EP3-EP2-EP1-3') is either extended at its 3' end to form a primer (5'-EP3-EP2-EP1-S'2-B-3') which can be used in subsequent amplification or otherwise degraded at its 3' end (5'-EP3-EP2-3') to render the probe inert during subsequent amplification. Col. 14, lines 36-44 generally describe the process of modifying the probe. While the initial probe and the extended primer include a stem/loop formation at their 5' ends formed by annealing of the EP3 region to the EP2 region, neither possess a stem/loop formation at their 3' ends. Thus, Western fails to overcome the deficiency of Cleuziat.

The PTO has cited, at pages 6-7 of the outstanding office action, a number of reasons why one of ordinary skill in the art generally would have been motivated to combine the teachings of Cleuziat and Western. Even assuming *arguendo* this to be true, which applicants do not admit, applicants submit that one of ordinary skill in the art would not have been motivated to replace the primers disclosed in Cleuziat with the primers disclosed in Western, since the primers in Western are not recited to possess a blocking agent, which Cleuziat requires (see Cleuziat, col. 11, lines 9-20). For this reason and the reasons noted above, Cleuziat effectively teaches away from the formation of a nucleic acid molecule with stem/loop formations at both its 3' end and its 5' end. Similarly, Western fails to provide any motivation for preparing a nucleic acid template which includes a stem/loop formation at its 3' and 5' ends, and the PTO has not cited any other motivation for doing so.

Even if one of ordinary skill in the art was to have combined the teachings of Western and Cleuziat, Western would not have overcome the deficiency of Cleuziat, because the combination thereof fails to teach or suggest a nucleic acid molecule including "a 3' end portion comprising a first region located 3' terminal and a first complementary region which, under suitable conditions, anneal to one another to form a first loop" and "a 5' end portion comprising a second region located 5' terminal and a second complementary region which, under suitable conditions, anneal to one another to form a second loop" as recited in step A) of both claim 29 and claim 51. Moreover, Cleuziat and Western similarly fail to teach or suggest a number of other limitations recited in these claims.

With respect to claim 29, in the absence of a nucleic acid which includes stem/loop formations at the 3' and 5' ends as recited in step A), neither Cleuziat nor Western, either alone or in combination, provides any suggestion to "extend[] the 3' terminal of the template to the 5' end of the template by means of a polymerase having strand displacement activity" as recited in step B). As a result of such extension, claim 29 recites the formation of a template extension "which includes a third region located 3' terminal and a third complementary region ... which, under suitable conditions, anneal to one another to form a third loop". Moreover, in the absence of a nucleic acid which includes stem/loop formations at the 3' and 5' ends as recited in step A), neither Cleuziat nor Western, either alone or in combination, provides any suggestion to "anneal[] to the first loop of the extended template an oligonucleotide primer" as recited in step C), let alone "extending the oligonucleotide primer along the extended template, by means of a polymerase having strand displacement activity, to form a new template complementary to the template" as recited in step D). Having failed to teach or suggest formation of a template extension in step B), neither

Cleuziat nor Western, either alone or in combination, teaches or suggests "further extending the 3' terminal of the extended template to the 5' end of the extended template by means of a polymerase having strand displacement activity, when the third region and the third complementary region are annealed to one another to form the third loop, thereby displacing the new template from the extended template" as recited in step E). Likewise, Cleuziat and Western, either alone or in combination, fail to teach or suggest repeating the process of steps A-E) using the displaced new template as the template in step A) for purposes of amplifying the nucleic acid. This is recited in step F) of claim 29. For all these reasons, therefore, applicants submit that the combination of Cleuziat and Western would not have rendered obvious the invention of claim 29 or any of claims 42-49 dependent thereon.

With respect to claim 51, in the absence of a nucleic acid which includes stem/loop formations at the 3' and 5' ends as recited in step A), neither Cleuziat nor Western, either alone or in combination, provides any suggestion to "extend[] the 3' terminal of the template to the 5' end of the template by means of a polymerase having strand displacement activity" as recited in step B). As a result of such extension, claim 51 recites the formation of a template extension "which includes a third region located 3' terminal and a third complementary region ... which, under suitable conditions, anneal to one another to form a third loop". Moreover, in the absence of a nucleic acid which includes stem/loop formations at the 3' and 5' ends as recited in step A), neither Cleuziat nor Western, either alone or in combination, provides any suggestion to "anneal[] to the first loop of the extended template an oligonucleotide primer" as recited in step C), let alone "extending the oligonucleotide primer along the extended template, by means of a polymerase having strand displacement activity, to form a new template complementary to the template" as recited in step D). Having failed to disclose an extended template as recited in step B) and a new template as formed in step D), neither Cleuziat nor Western, either alone or in combination, teaches or suggests "displacing the new template from the extended template" as recited in step E) of claim 51. For all these reasons, therefore, applicants submit that the combination of Cleuziat and Western would not have rendered obvious the invention of claim 51 or any of claims 52-59 dependent thereon.

Thus, the rejection of claims 29-41 and 45-50 under 35 U.S.C. § 103(a) for obviousness over Cleuziat in view of Western is improper and should be withdrawn.

The rejection of claims 29-50 under 35 U.S.C. § 103(a) for obviousness over Cleuziat in view of Western and U.S. Patent No. 6,025,139 to Yager et al. ("Yager") is respectfully traversed.

Cleuziat and Western are cited substantially as described above.

Yager relates to a ligase-based assay that utilizes a set of linear oligonucleotide probes which, when matched perfectly to a target sequence, afford a ligation product of predictable size. The PTO cites to Yager for teaching use of betaine as a melting temperature regulator. However, Yager fails to overcome the above-noted deficiencies of Cleuziat and Western.

Therefore, rejection of claims 29-50 under 35 U.S.C. § 103(a) for obviousness over Cleuziat in view of Western and Yager is improper and should be withdrawn.

During the December 4, 2001, personal interview, applicants demonstrated an animation to illustrate the presently claimed invention. The drawings, of course, illustrate distinct steps in the claimed process, whereas the animation depicts the continuity of the claimed process as performed. During the course of the interview, it was noted that one version of the animation is available on an Internet site of Eiken Chemical Co. Ltd., assignee of the present invention. Applicants attorneys have inquired into the date on which the animation became publicly available via the above-referenced Internet site and determined that the animation was not available until after the priority filing date for the present application.

In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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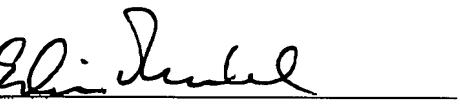

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